



UNIVERSITÉ DE
SHERBROOKE

Fibromyalgia Update: long term outcomes & heterogeneity clinical manifestation

Juliana Barcellos de Souza, pht, PhD



Disclosure Statement



2003-2007



2008

Presentation plan

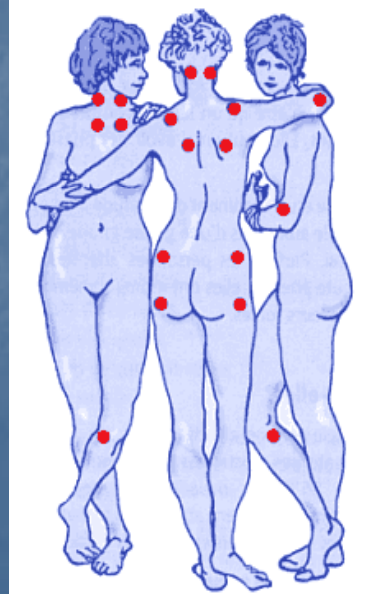
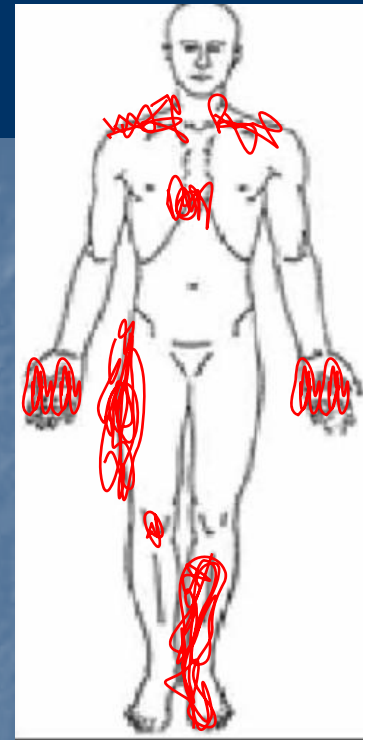
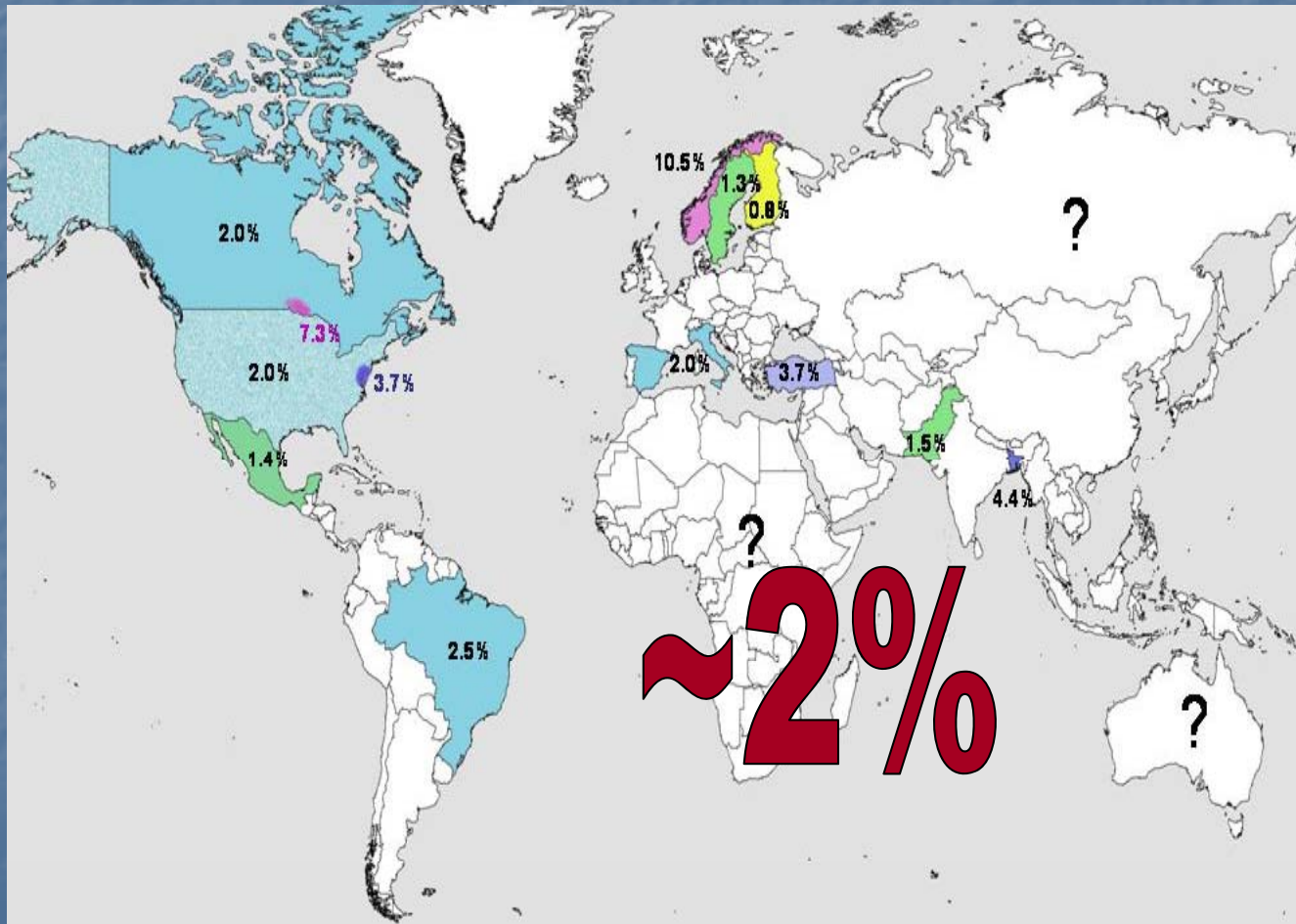
Context: Fibromyalgia

- Diagnostic criteria
- Prevalence
- Symptoms
- Fibromyalgia etiologies

Treatment : long term outcomes

Clinical manifestation: Heterogeneity

Introduction



Which symptoms?

Fibromyalgia: Symptoms

Tableau 2 : Prévalence des symptômes associés à la fibromyalgie

Symptômes	Wolfe ¹ 1990	Yunus ² 1993	Kennedy ⁴ 1983 1996	Autres 199	Nöller ⁵ 2003	Bernatsky ⁷ 2005	Weir ⁴ 2006	Autres 200
Douleur diffuse	98 %	100%	59% Intense	55% Intense	77% ¹³ musculaire	100%		
Fatigue	78 à 85%	86%		59% Intense	77% ¹³	88%	RR ♂ = 5.64 (Syndrome de fatigue chronique) (4%)	
Fatigue matinale	76 à 78%	78%						
Trouble du sommeil	73 à 76%	65%	14% Intense	48% Intense	66% ¹³ 56% ¹³ insomnie	88%		
Raideur		78%						
Anxiété	45 à 51%	62%				1%	RR ♂ = 3.47 (22%)	
Dépression		34%			70% ¹²	5%	RR ♂ = 2.85 (8%)	40% ⁸ 29% ¹⁰ 87% ¹¹ 90% ⁶
Troubles système digestif (SCI)	36 à 22%	40%			60% ³	36%	RR ♂ = 4.45 (13%)	Romell 63% ⁸ Romell 81% ⁸
Migraine ou maux de tête	54 à 51%	53%					RR ♂ = 3.47 (migraine) (64%)	

1 Wolfe et al, 199 ; 2 Yunus et al, 199 ; 3 Veale et al 1991 et Sivri et al. 1996; 4 Kennedy, 1996; 5 Nöller, 2003; 6 Guven, AZ 2005; 7 Bernatsky, 2005; 8 Kurland et al., 2006; 10 Rao 2003; 11 Kochman 2003; 12 Epstein 1996; 13 White et al. 1999; 14 Weir et al 200

Which causes?

Fibromyalgia: model of causes

Tableau 1: Les modèles conceptuels de la Fibromyalgie (FM)

Modèle étiologique	Musculaire	Psychologique	Génétique	Neurophysiologique
Causes	<p>Inflammation des muscles ou des tissus conjonctifs</p> <p>Irritation chimique ou mécanique aux muscles</p> <p>Trouble du métabolisme oxydatif :</p> <p>Altered muscular methabolism</p>	<p>Hypervigilance par un événement déclencheur</p> <p>Le milieu comme une source d'apprentissage aux réponses pessimistes</p> <p>Le milieu comme réducteur des tentatives</p> <p>Affective disturbs</p> <p>stress</p> <p>motivo</p> <p>affectifs (Dépression masquée)</p> <p>Syndrôme du stress post-traumatique</p>	<p>Trouble neurophysiologique (ex.: dopamine et sérotonine)</p> <p>Familles avec des seuils de douleur plus bas</p> <p>Agrégation familiale de la fibromyalgie</p> <p>Lower pain threshold families</p>	<p>Trouble du sommeil (Hormone de</p> <p>Neurochemical imbalances</p> <p>Sleep disturbances</p> <p>noradrénaline, dopamine: hausse de</p> <p>Autonomy nervous system dysfunction</p> <p>Trouble de concentration</p> <p>deficit on DNIC</p> <p>Prédominance sympathique</p> <p>Wind-up et Déficit du CIDN</p>
Symptômes	<p>Douleur</p> <p>Réduction de la force musculaire</p> <p>Réduction de la performance musculaire</p> <p>Fatigue</p> <p>Raideur</p>	<p>Dépression</p> <p>Anxiété</p> <p>Hypervigilance</p> <p>Douleur psychologique (composante motivo-affective)</p>	<p>Bas seuil de douleur</p>	
Limites	<p>Facteurs confondants :</p> <p>Kinésiophobie</p> <p>Métabolisme global semble être normal</p> <p>Déconditionnement aérobie</p> <p>Manque de rigueur méthodologique aux études morphologiques</p> <p>Anormalités histologiques limitées pour expliquer la cause de la douleur</p>	<p>Évènement déclencheur de la FM : cause ou coïncidence (?)</p> <p>FM idiopathiques</p> <p>FM sans trouble de l'humeur</p> <p>Inefficacité des traitements pharmacologiques (anti-dépresseurs)</p>	<p>Interaction génétique et phénotype</p> <p>L'environnement peut influencer la manifestation génétique</p>	

Multidisciplinary program

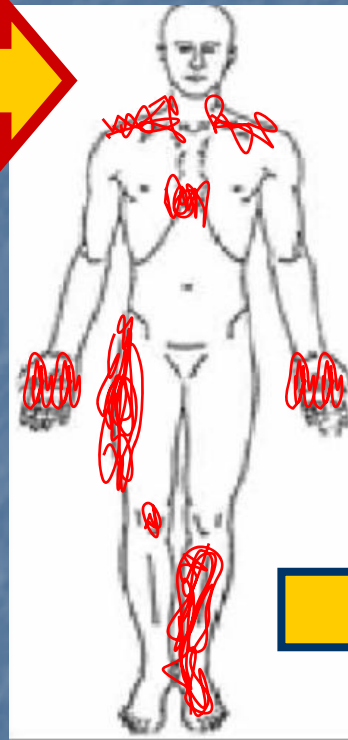
Pain

Stiffness

Fatigue

Mood disorder

Sleep disturbs



Physical activity

Relaxation techniques

Massages

Education

Nutrition

Psychological approaches (CBT)

Fibromyalgia Symptoms' variability

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graph TD; A[Fibromyalgia Symptoms' variability] --> B[Treatment (?)]; A --> C[Heterogeneity (?)]
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Treatment (?)

Heterogeneity (?)

Fibromyalgia Symptoms' variability



Treatment (?)

Heterogeneity (?)

Multidisciplinary treatments

Programmes multidisciplinaires incluant un suivi à long terme

Étude	Programme	Résultats			
		immédiat	Suivi à long terme (plus que 6 mois)		
(Bennett <i>et al.</i> , 1996)	6 mois (1 fois par semaine) (A) Multidisciplinaire : discussion en groupe (10 patients), stratégies de gestion du stress, exercices, soutien aux familles. (n=170). (B) Groupe contrôle (n=170) Abandons : 39%	<p>Long term follow-up</p> <p>FIQ Scores</p> <p>QOL Scores</p> <p>● FIQ results</p> <p>■ QOL results</p> <p>Program start Program end 12 months 18 months 24 months</p>			
(Wigers <i>et al.</i> , 1996)	14 semaines (A) Exercices (60-70%F) (B) Gestion du stress (n=100) (C) Groupe contrôle (n=100) Abandons : (A) 25%, (B) 33%; (C) 18%			(B) moins dépressif	<p>au suivi de 2-ans : les améliorations se maintiennent.</p> <p>Abandons : 81%</p> <p>Aucune amélioration ne se maintient au suivi (4,5 ans)</p>
(Buckelew <i>et al.</i> , 1998)	6 semaines à 2 ans (A) Relaxation + Biofeedback (n=29) (B) Exercices (n=30) (C) Combinaison (A) + (B) (n=30) (D) Éducation (contrôle) (n=30) Abandons : non indiqués			(A) (B) et (C) : augmentation de l'activité physique, de la perception d'efficacité, amélioration du sommeil et réduction de la douleur et des comportements douloureux. (B) et (C) : moins de détresse psychologique	(C) présente les meilleurs résultats au suivi de 2 ans. (A) et (B) obtiennent aussi des résultats favorables

Multidisciplinary treatments

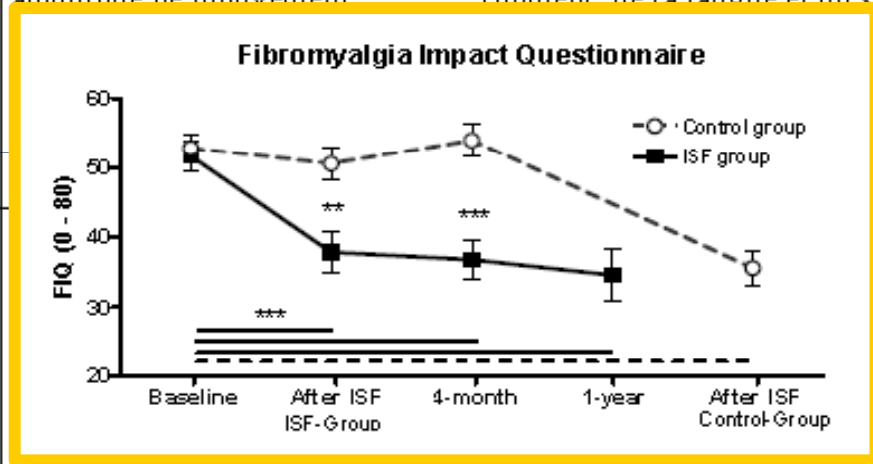
Étude	Programme	Résultats	
		immédiat	Suivi à long terme (plus que 6 mois)
(Mannerkorpi <i>et al.</i> , 2002)	6 mois (A) Éducation + exercices dans l'eau (piscine) (n= 37) (B) Groupe contrôle (n=32) Abandons: (A) 24%, (B) 6 %	(A) réduction du FIQ, MPI, points de sensibilité. Amélioration aux six minutes de marche, SF-36, amplitude de mouvement, endurance et force musculaire.	Groupe (A) : la performance aérobique, la fonctionnalité physique, la réduction de la douleur, de la fatigue et du stress se maintiennent au suivi de 6 mois. Douleur, fatigue et fonctionnalité sociale sont maintenues au suivi de 2 ans.
(Lemstra <i>et al.</i> , 2005)	6 semaines (24 rencontres) (A) Exercice+ contrôle du stress+ éducation+ discussions en groupes + massages + discussions nutritionnelles (n=43) (B) Groupe contrôle (n=36) Abandons : (A) 16% (B) 0%	(A) amélioration de la perception d'efficacité, réduction de la douleur, amélioration de l'humeur.	La plupart des changements acquis durant le traitement se maintiennent au suivi de 15 mois. Ils observent un lien entre l'amélioration des patients et l'adhésion aux exercices. Abandons: (A) 19%

Poor long-term success and high abandon rate

- Objective treatment (Evers et al, Pain, 2002)
- Therapeutic alliance (Dobkin et al JRheum 2006, Mannerkorpi et al JRheum 2000)
- Compliance with physical activity programs (Redondo et al JRheum 2004, Dobkin et al ClinJPain 20006)
- Psychological impact of FM (Jensen et al Pain 2004)

Multidisciplinary treatments

Étude	Programme	Résultats	
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(Souza <i>et al.</i> , 2007)	11 semaines (9 rencontres) (A) École interactionnelle de fibromyalgie (n=30) (B) liste d'attente (n=30) Abandon (A) 3%	(A) réduction du FIQ, MPI, PCS, points de sensibilité. Amélioration aux SF-36.	acqui ...ennent



FIQ = Fibromyalgia Impact Questionnaire; QOL = SF-36 = Quality of life / Qualité de vie FC = fréquence cardiaque

École interactionnelle de fibromyalgie : description et évaluation

Interactional school of fibromyalgia: description and evaluation

J. Barcellos de Souza, J. Charest, S. Marchand

ARTIGO ORIGINAL
ORIGINAL ARTICLE

Escola Inter-relacional de Fibromialgia: Aprendendo a Lidar
com a Dor – Estudo Clínico Randomizado

*Interactional School of Fibromyalgia: Learning to Cope with Pain –
a Randomized Controlled Study*

Juliana Barcellos de Souza^(*), Patricia Bouryauk^(**), Jacques Charest^(**), Serge Marchand^(**)

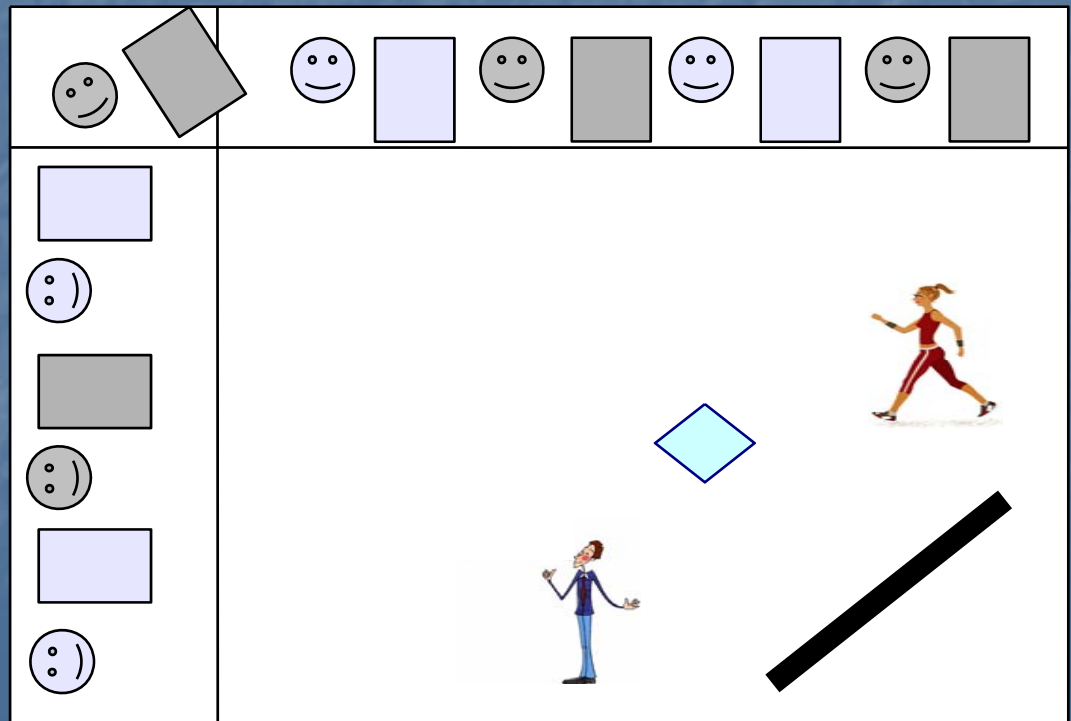
Interactional School of Fibromyalgia

Group treatment:

8 patients + 2 health care professionals

**Nine meetings
(11 weeks)**

2 hours / meeting



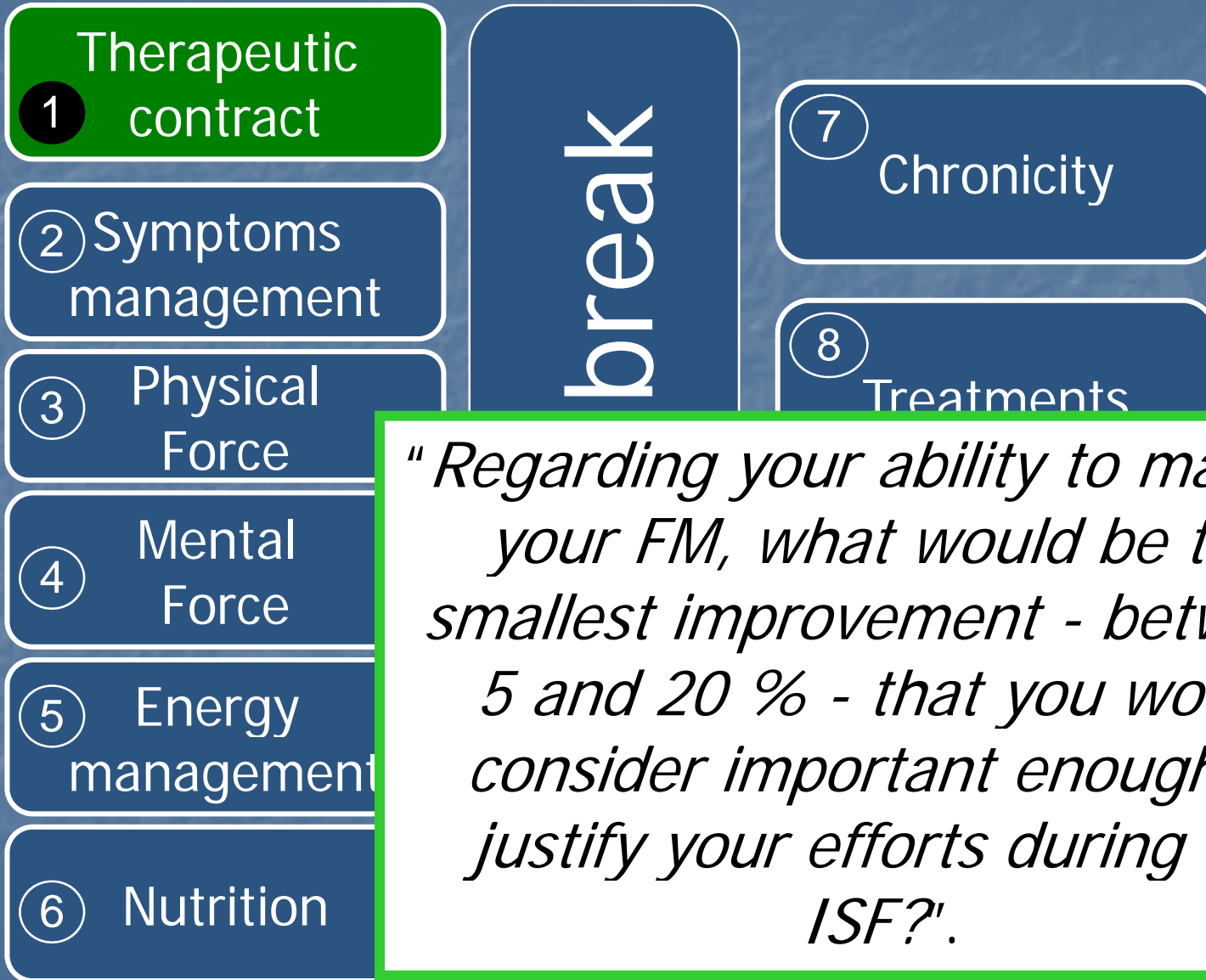
Interactional School of Fibromyalgia

- 1 Therapeutic contract
- 2 Symptoms management
- 3 Physical Force
- 4 Mental Force
- 5 Energy management
- 6 Nutrition

2 weeks break

- 7 Chronicity
- 8 Treatments
- 9 Retrospective

Interactional School of Fibromyalgia



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Interactional School of Fibromyalgia

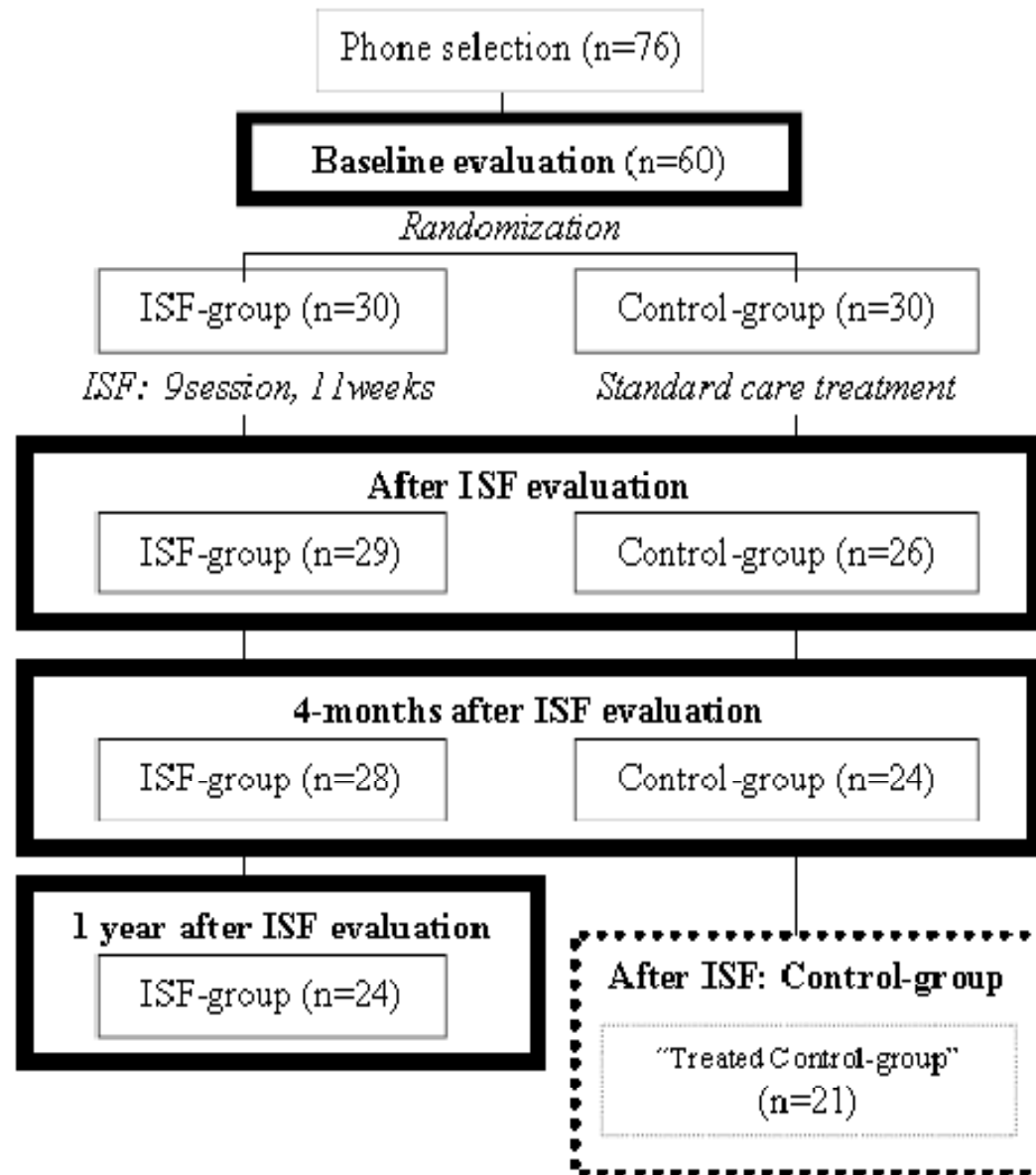
- 1 Therapeutic contract
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- 4 Mental Force
- 5 Energy management

6 weeks break

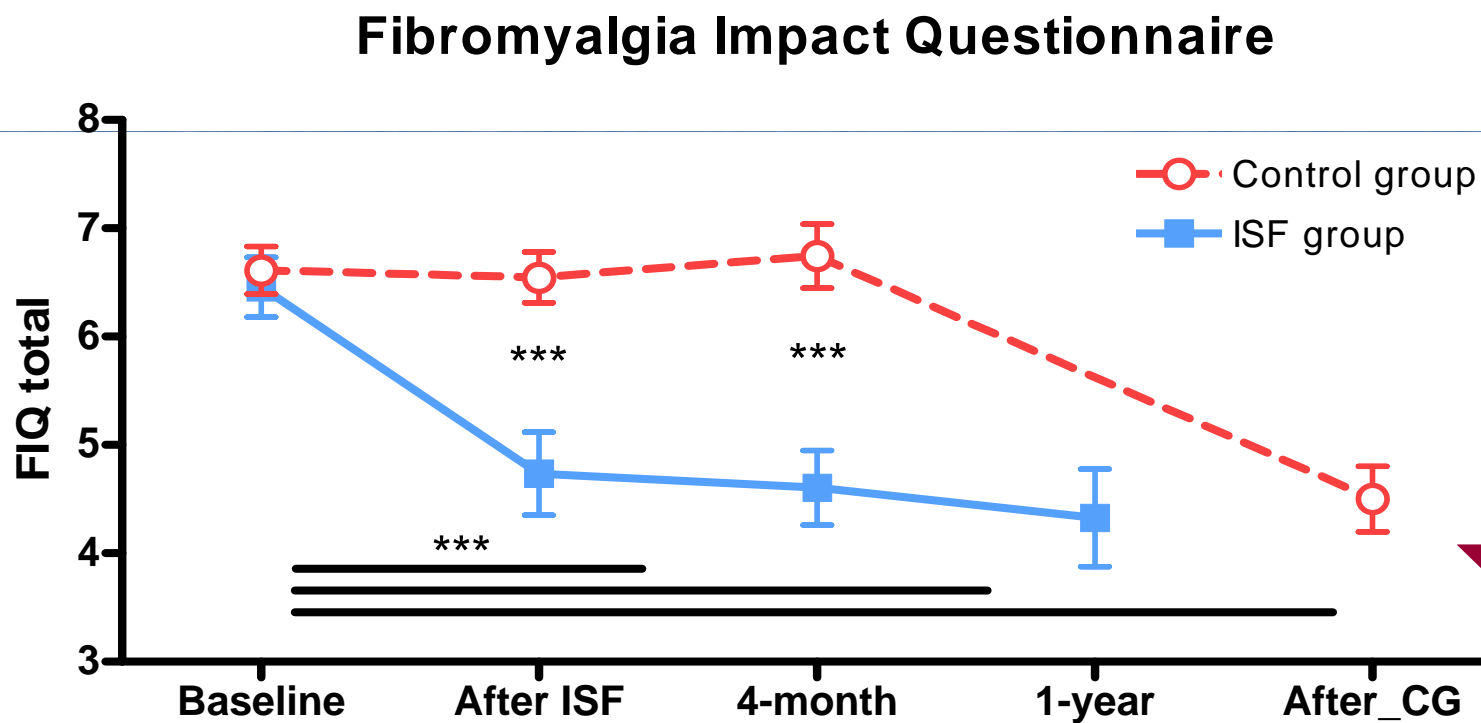
- 7 Chronicity
- 8 Treatments
- 9 Retrospective

"What could you do to put yourself back into your initial condition, before you started the ISF?"

Study design

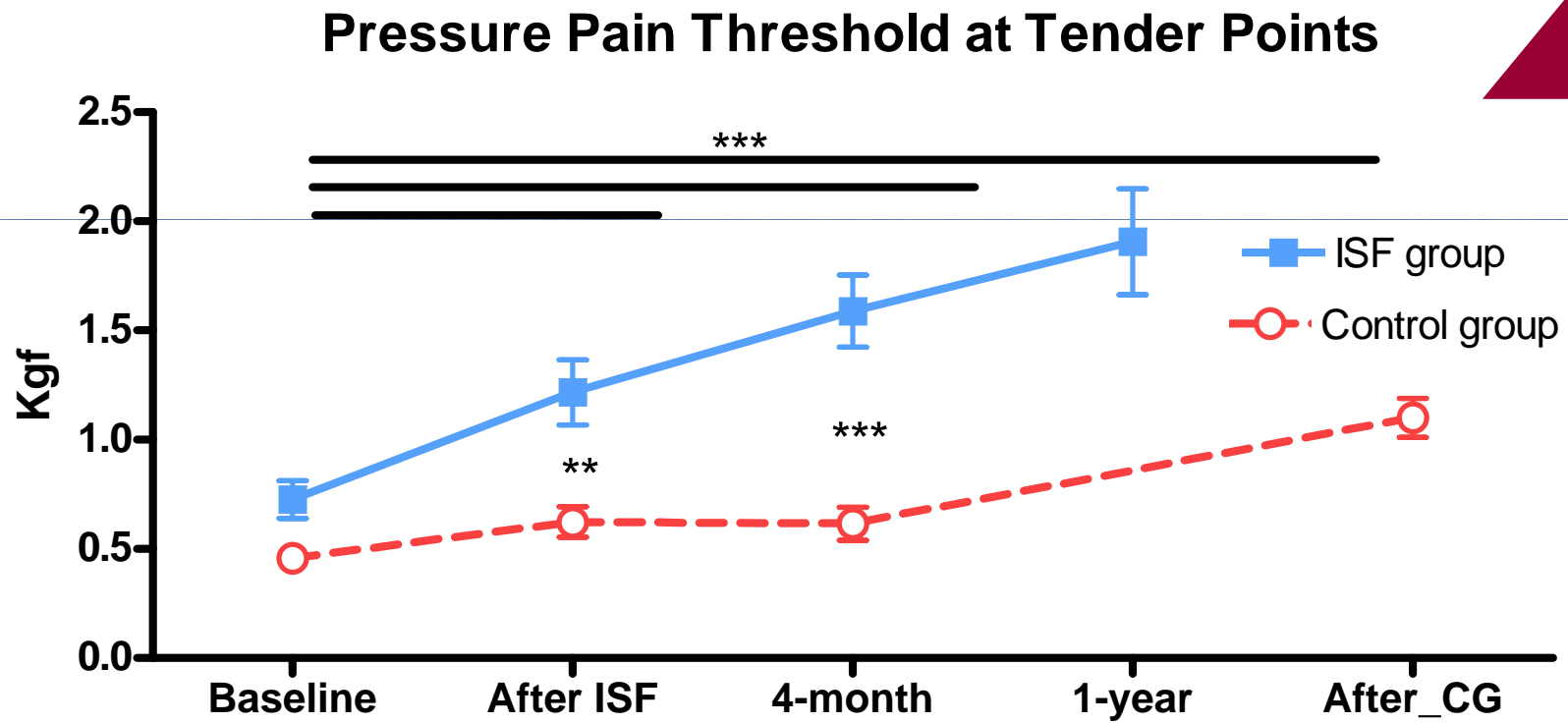


Outcomes short and long term



Lower impact
(Better)

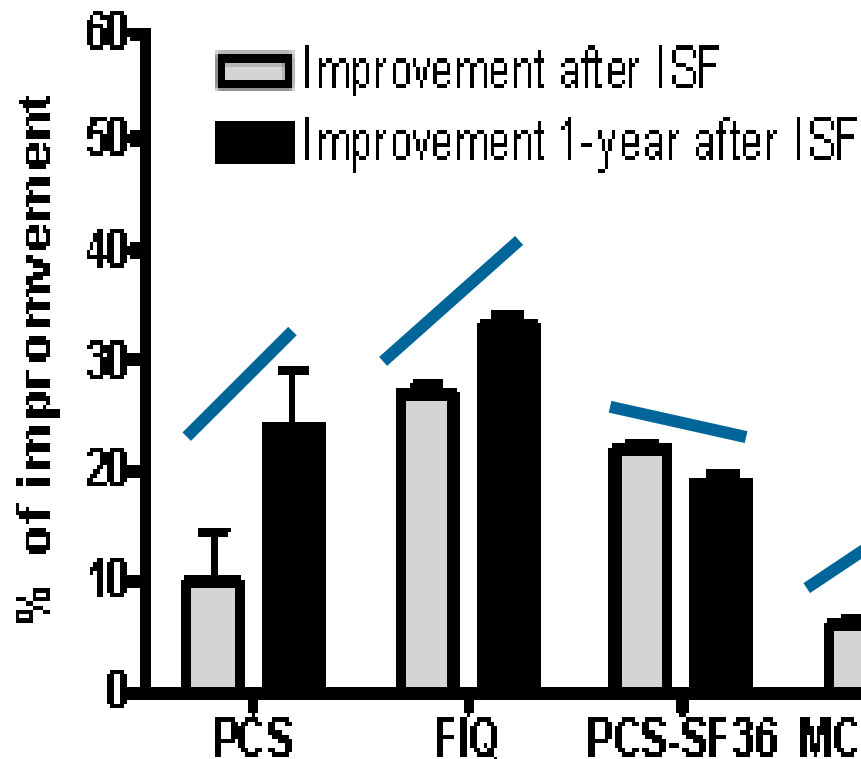
Outcomes short and long term



Higher Threshold
(Better)

Outcomes short and long term

Percentage of Improvement after the ISF and at 1-year follow up comparing to baseline



PCS: 10% to 24%

FIQ: 27% to 33%

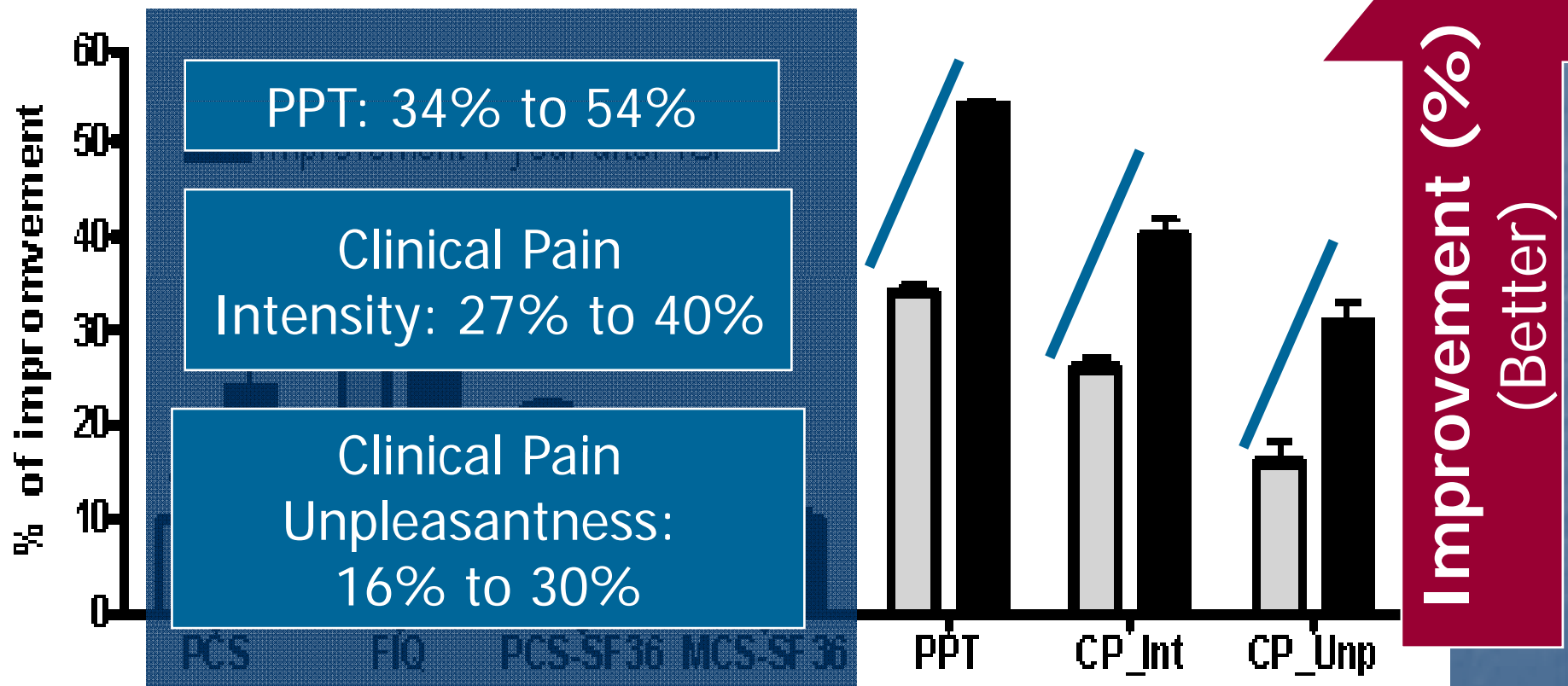
SF-36-PCS: 22% to 19%

SF36-MCS: 6% to 10%

Improvement (%)
(Better)

Outcomes short and long term

Percentage of Improvement after the ISF and at 1-year follow up comparing to baseline



Intent-to-treat analyses

Table 4: Intent-to-treat and analyses of completers 1-year follow-up for the ISF-group

Variable	Baseline	1-year after the ISF		Intent-to-treat principle	
	ISF group n=30	ISF group n=24		1-year after the ISF ISF group n=30	
	Mean (Sd)	Mean (Sd)	p-value	Mean (Sd)	p-value
Clinical pain					
Intensity	45,11 (19.88)	27.59 (17.76)	<0.001	34,71 (22.02)	0.001
Unpleasantness	41.80 (21.91)	25.01 (18.29)	0.003	33.24 (24.38)	0.006
FIQ					
Physical Functioning	4,08 (1,62)	2,06 (1,67)	0.011	2,53 (1,87)	<0.001
Pain	7,03 (1,80)	5,40 (3,20)	0.003	5,81 (2,91)	0.009
Fatigue	7,44 (1,57)	5,93 (2,96)	0.001	6,09 (2,74)	0.002
Morning Tiredness	7,28 (1,99)	5,04 (2,99)	NS	5,41 (2,78)	0.003
Stiffness	7,61 (2,16)	5,08 (3,18)	0.018	5,56 (2,95)	<0.001
Anxiety	6,21 (2,74)	3,66(2,37)	NS	4,38 (2,66)	0.003
Depression	5,24 (2,99)	3,07 (2,57)	0.011	3,74 (2,76)	0.004
PPT	0.69 (0.46)	1.91 (1.16)	<0.001	1.70 (1.10)	<0.001
SF-36					
MCS-SF36	38.95 (12.58)	48.08 (8.79)	NS	44.90 (12.03)	0.010
PCS-SF36	30.28 (5.89)	39.36 (9.81)	0.020	38.00 (8.62)	<0.001
PCS*	1,90 (1,09)	0,82 (0,69)	NS	1,29 (0,99)	0.050

* n=15 at baseline and n=10 at 1 year follow-up, non-parametric test

Legends:
Physical C
Pressure P

CS-SF36:
36; PPT:

Improvement is maintained!

Fibromyalgia Symptoms' variability

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graph TD; A[Fibromyalgia Symptoms' variability] --> B[Treatment (?)]; A --> C[Heterogeneity (?)];
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Treatment (?)

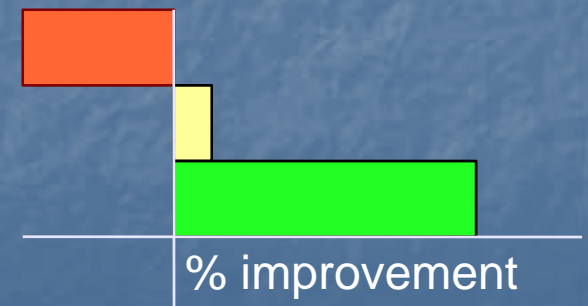
Multidisciplinary treatment
Many health care professional
Expensive and long programs
Lower adherence rate
Long term effect

Heterogeneity (?)

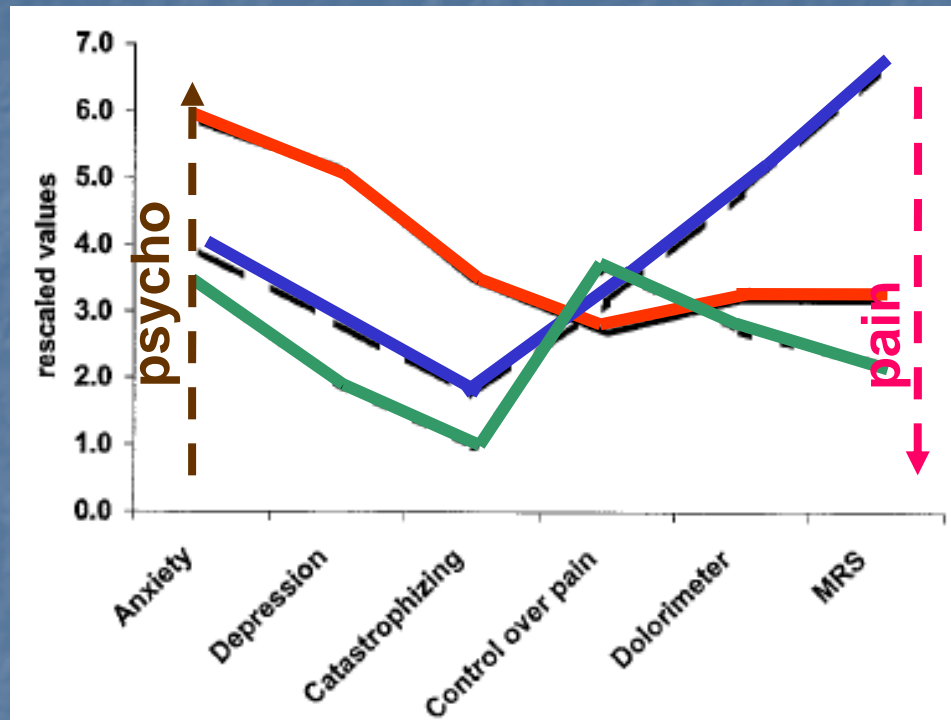
Which groups ?
Complex models
Clinical application

FM Inter-patients variability

- **Symptoms characteristics**
 - Psychological
 - Pain
 - Pain Catastrophic thinking
- **Outcomes**
 - Pharmacologic treatments
 - Non pharmacologic treatments
 - Multidisciplinary



Inter-patients variability



Group 1 (n=50)

- Low tenderness
- Moderate depression/anxiety
- Moderate catastrophizing
- Moderate control over pain



Group 2 (n=31)

- High tenderness
- High depression/anxiety
- High catastrophizing
- Low control over pain

Group 3 (n=16)

- High tenderness
- Low depression/anxiety
- Low catastrophizing
- High control over pain

Limits:

Group 1: low FM symptoms (similar to healthy subjects?)

Many measures = complex clinical application

No clinical measures (subjective measures)

Giesecke et al, 2003

Table 2. Cluster characteristics*

Variable	Cluster 1	Cluster 2	Cluster 3
Age, years	46.1 ± 10.0	42.8 ± 11.3	45.5 ± 9.6
MRS, kg	6.63 ± 1.7	3.22 ± 1.4	2.24 ± 1.3
Dolorimeter, kg	4.81 ± 2.2	3.21 ± 1.7	2.73 ± 1.3
CES-D score	14.10 ± 7.5	23.74 ± 7.5	9.63 ± 4.0
CTDI	10.76 ± 4.0	20.12 ± 8.5	17.66 ± 6.0

FM subgroups: is it possible to access them using a single and simple questionnaire?

Rheumatol Int

DOI 10.1007/s00296-008-0722-5

ORIGINAL ARTICLE

Fibromyalgia subgroups: profiling distinct subgroups using the Fibromyalgia Impact Questionnaire. A preliminary study

**Juliana Barcellos de Souza · Philippe Goffaux ·
Nancy Julien · Jacques Charest · Serge Marchand**

Classification variables

VAS FIQ sub scales

*Pain, Fatigue, Stiffness, Morning Tiredness,
Anxiety, Depression*



Data analyses

Cluster classification analyses

Type: Hierarchical

(Sq. Eucliden dist., Ward`s method: Aldenderfer et al., 1984; Milligan et al. 1985)

Each subject =
one cluster

1

2

3

4

4

Similar "classification variables"
= patients groups

1

4

3

2

3

1

4

3

2

2

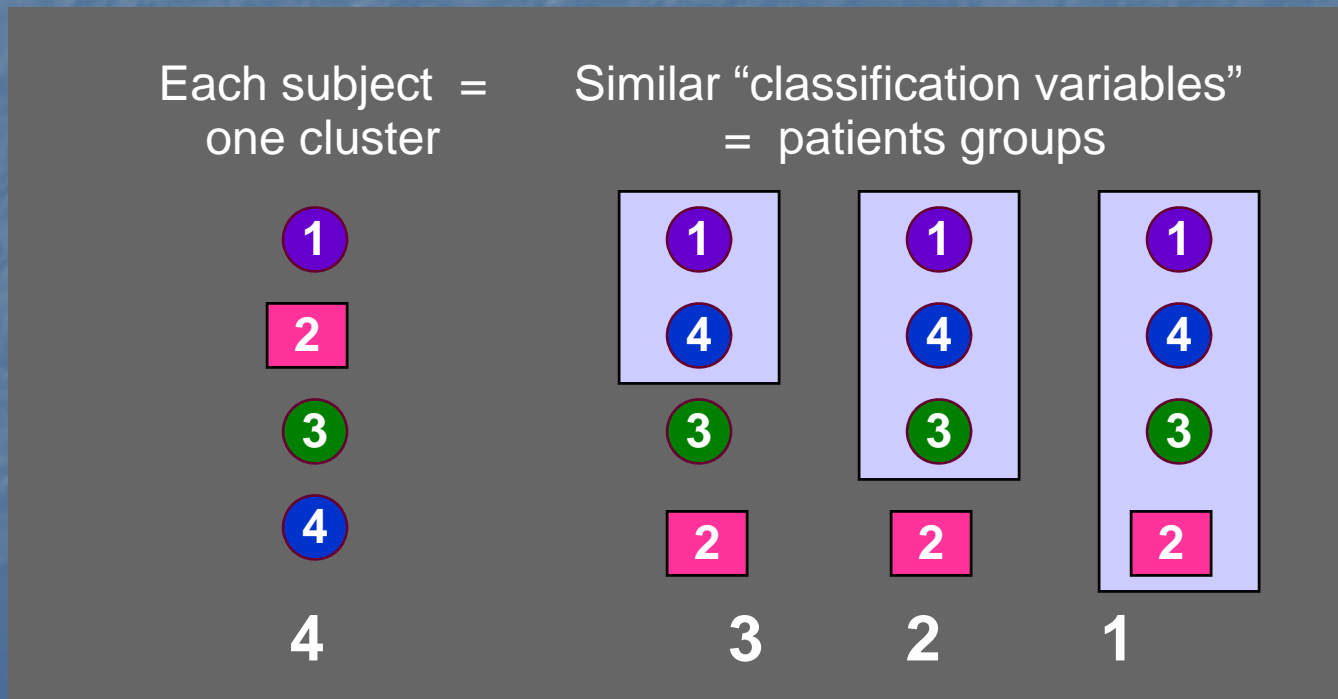
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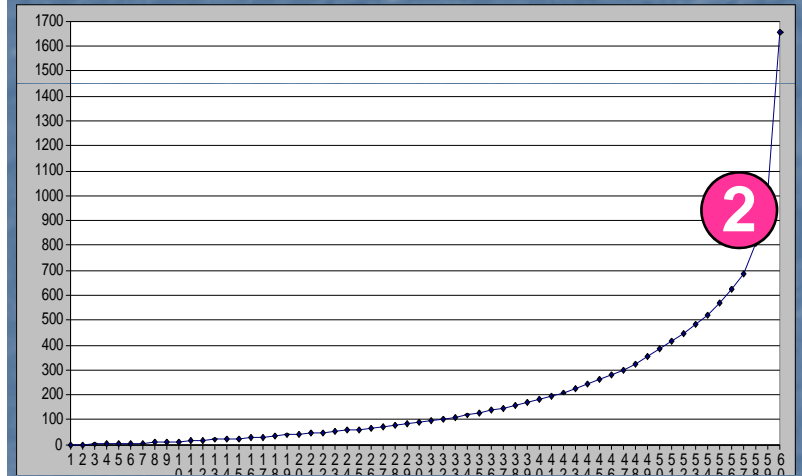
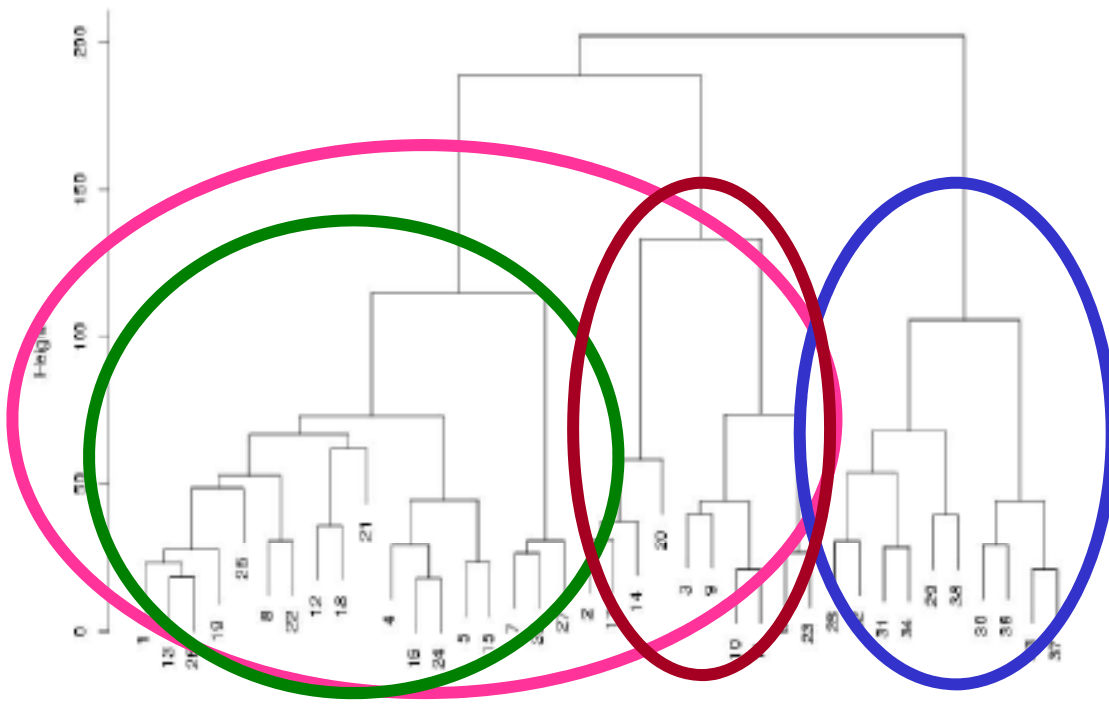
3

2

1



Cut point criteria



We used:

Agglomeration coefficient

Stepsize Criteria

Calinski & Harabasz Index

Fibromyalgia profiles using VAS subscales of the FIQ

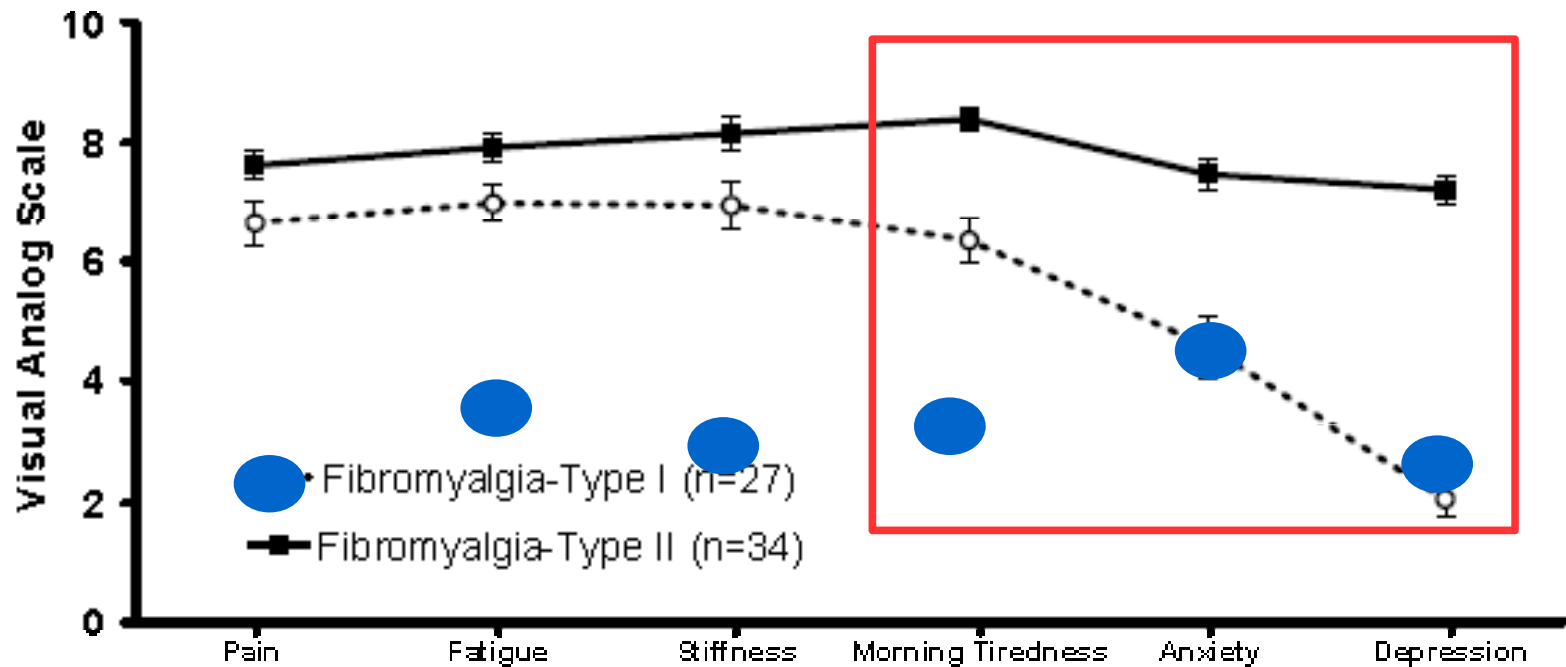


Figure 1: Clusters created using the visual analogue subscales of the FIQ

Table 2: Cluster Characteristics

FIQ subscales	FM-Type I Mean (S.D.) (n=27)	FM-Type II Mean (S.D.) (n=34)	Saturation Loadings	Classification Function Coefficients	
				FM-Type I	FM-Type II
Pain	6.65 (2.01)	7.62 (1.41)	0.144	1.837	1.975
Fatigue	6.99 (1.58)	7.92 (1.26)	0.167	2.230	1.452
Stiffness	6.95 (2.20)	8.15 (1.53)	0.164	0.522	0.097
Morning tiredness	6.35 (1.89)	8.39 (1.14)	0.341	1.782	2.998
Anxiety	4.58 (2.72)	7.47 (1.49)	0.345	0.050	0.035
Depression	2.07 (1.53)	7.22 (1.37)	0.904	-0.459	2.312
Constant				-21.827	-35.315

Print in boldface indicates the variables that most distinguish the clusters (with the highest saturation loadings).

Table 3: Multivariate Analysis of Demographic Data

Variables	FM-Type I Mean (S.D.) (n=27)	FM-Type II Mean (S.D.) (n=34)	F_{univariate}	p-value
Age (yr)	51.3 (7.2)	48.1 (7.3)	F= 2.64	p=0.11
Years with symptoms of chronic pain	12.2 (7.7)	12.5 (9.4)	F=0.009	p=0.92
Years with Fibromyalgia diagnosis	6.6 (4.4)	6.4 (6.0)	F=0.002	p=0.97
At work (full or part- time)	24%	20%	F=1.090	p=0.30
Idiopathic FM	15%	23%	F=2.448	p=0.12

Table 4: Multivariate Analysis of Psychosocial Data

Questionnaires	FM-Type I	FM-Type II	$F_{univariate}$	p-value	Effect size
	Mean (S.D.) (n=20)	Mean (S.D.) (n=25)			
PCS	21.665 (10.42)	30.16 (13.01)	F=5.820	p=0.02	0.72
Interference*	4.18 (0.80)	5.06 (0.60)	F=13.64	p<0.01	1.26
Life Control*	3.68 (0.91)	2.96 (1.20)	F=4.893	p=0.03	0.68
Support from significant others*	3.73 (1.30)	3.77 (1.82)	F=0.006	p=0.94	0.03
Mental Component Summary**	45.42 (9.46)	33.21 (11.0)	F=24.20	p<0.01	1.19
Physical Component Summary **	30.14 (6.10)	30.84 (5.68)	F=1.925	p=0.18	0.12

* MPI sub scale

** SF-36 sub scale

Values in boldface indicate that the variable differs significantly between clusters.

PCS: Pain Catastrophizing Scale; SF-36: Short-Form Healthy Survey.

Univariate effect sizes were only provided in Table 4 because, here, the multivariate analysis was significant and required univariate tests at follow-up.

Are FM-subgroups equivalent for patients from the **community** and those from a **Tertiary care multidisciplinary pain clinic?**



Marchand, S; Charest, J; Souza, JB

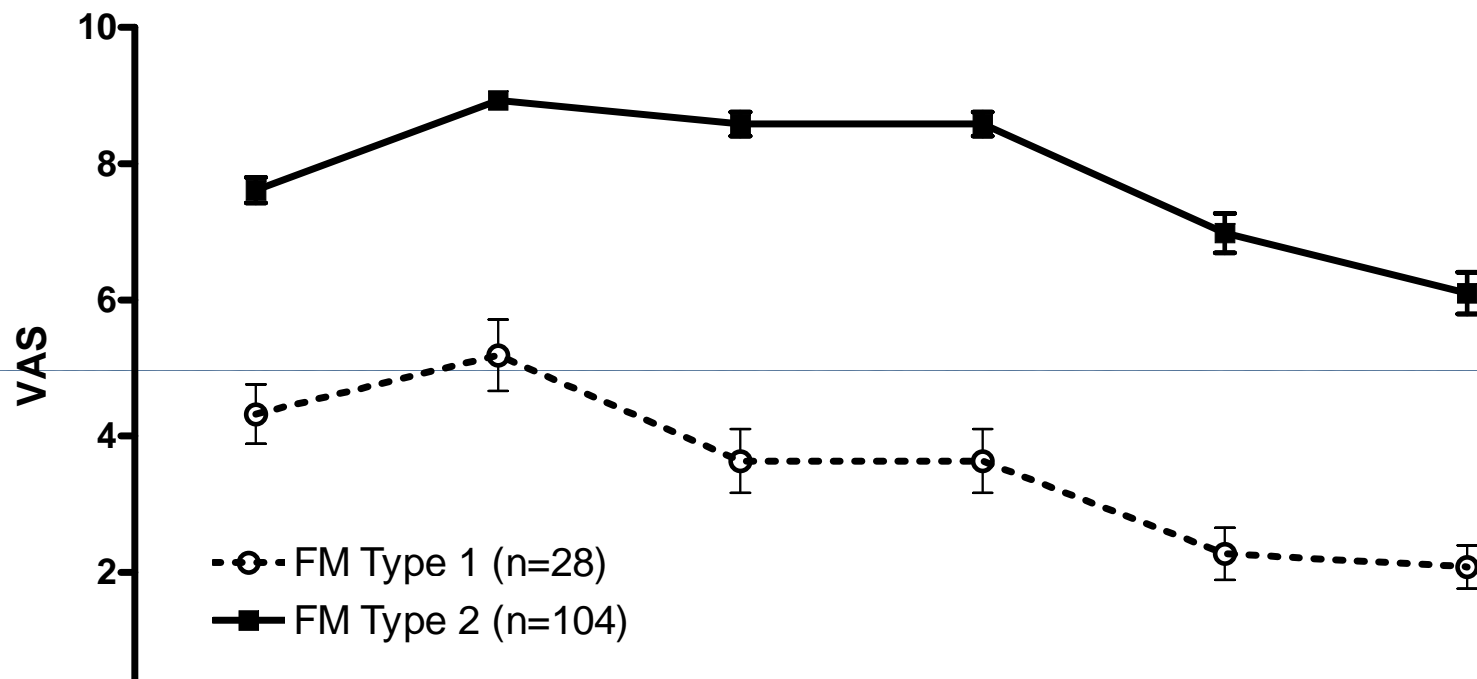


Fitzcharles, Mary-Ann

Community X Tertiary care multidisciplinary pain clinic

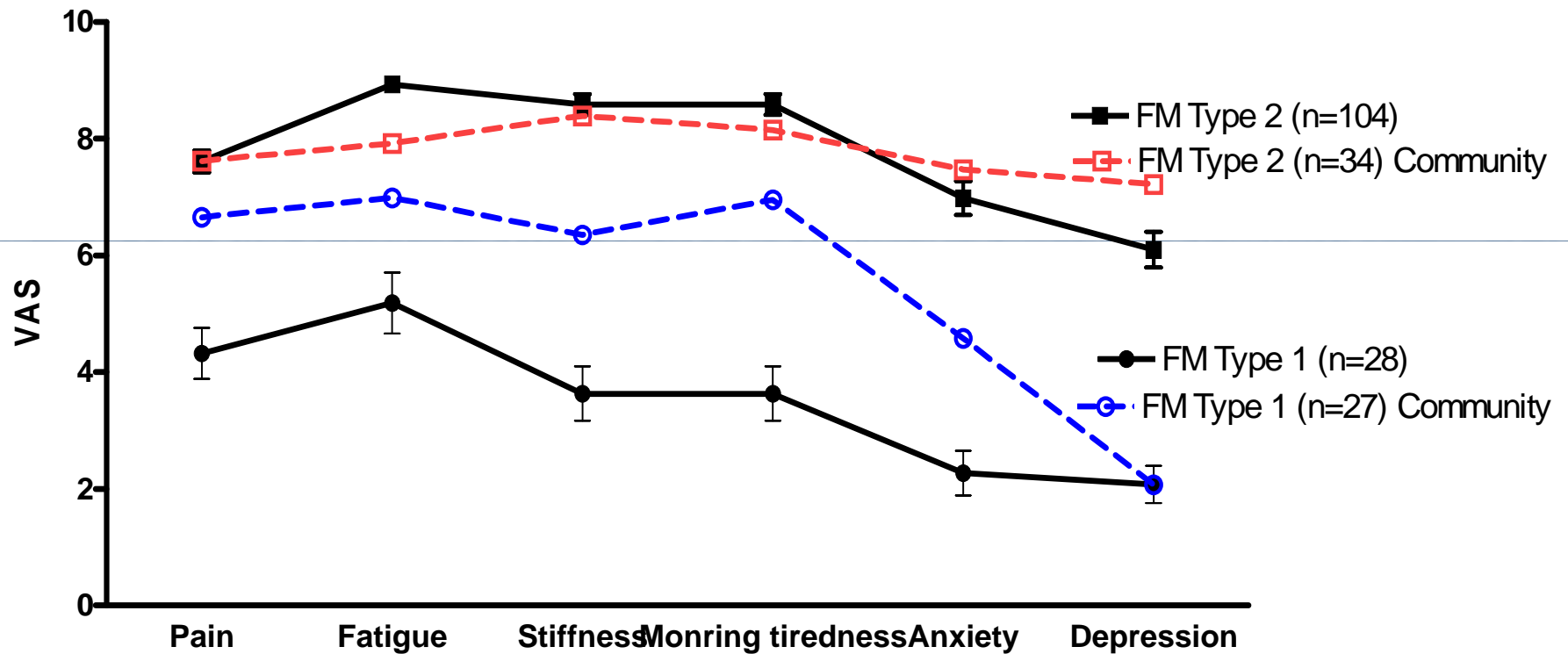
- N= 132 FM patients (TCMPC)
 - [61 FM patients from community]
- Analyses
 - (A) patients were assigned to the respective previous cluster proposed (Souza et al., Rheum. Int. 2008)
 - (B) cluster analysis was reapplied with this new sample. To confirm the number of clusters with this new cluster analysis

FM subgroups - Tertiary care multidisciplinary pain clinic



FM Type II Younger (47 Vs 53 years old)
Higher values for McGill Pain Questionnaire
Health Assessment Questionnaire
Pain Catastrophizing Scale
Pain Disability Index

FM subgroups - Tertiary care multidisciplinary pain clinic Versus Community



sensitivity of 0.96 PPV 0.41
 specificity of 0.71 NPV 0.99

Souza, Marchand, Fitzcharles, et al. In preparation

FM subgroups differs on pain control?
- neurophysiological model -

ORIGINAL ARTICLE

The Deficit of Pain Inhibition in Fibromyalgia Is More Pronounced in Patients With Comorbid Depressive Symptoms

Juliana Barcellos de Souza, PhD, Stéphane Potvin, PhD,* Philippe Goffaux, PhD,*
Jacques Charest, PhD,† and Serge Marchand, PhD*†*

FM subgroups differs on pain control?

- 55 FM women & 10 Healthy women
- Thermal stimuli
- Spatial summation paradigm
- Pressure pain threshold
- Clinical pain (VAS)

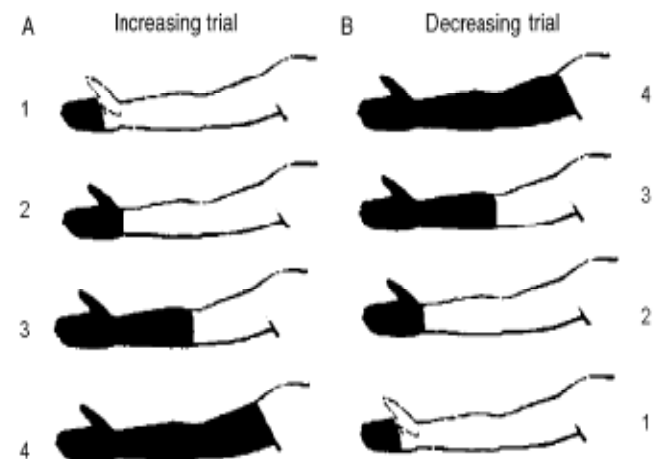
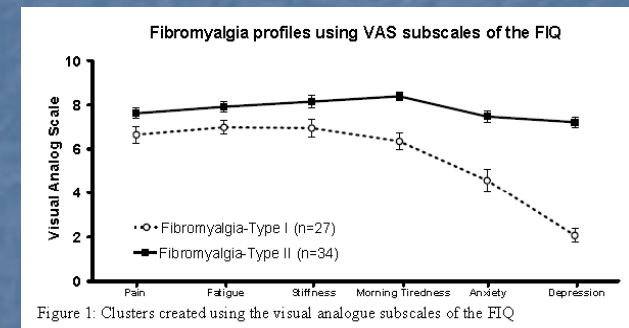


FIGURE 1. Schematic representation of the spatial summation procedure. A. Increasing trial. The 4 segments of the arm surface were sequentially stimulated for 2 minutes, from the fingers (1) to the shoulder (4), with 2-minute pauses between each stimulation.

(Marchand et al. 2002; Julien et al. 2005)

Thermal pain threshold

HW > FM-Type I and II

Pressure pain threshold

HW > FM-Type I and II

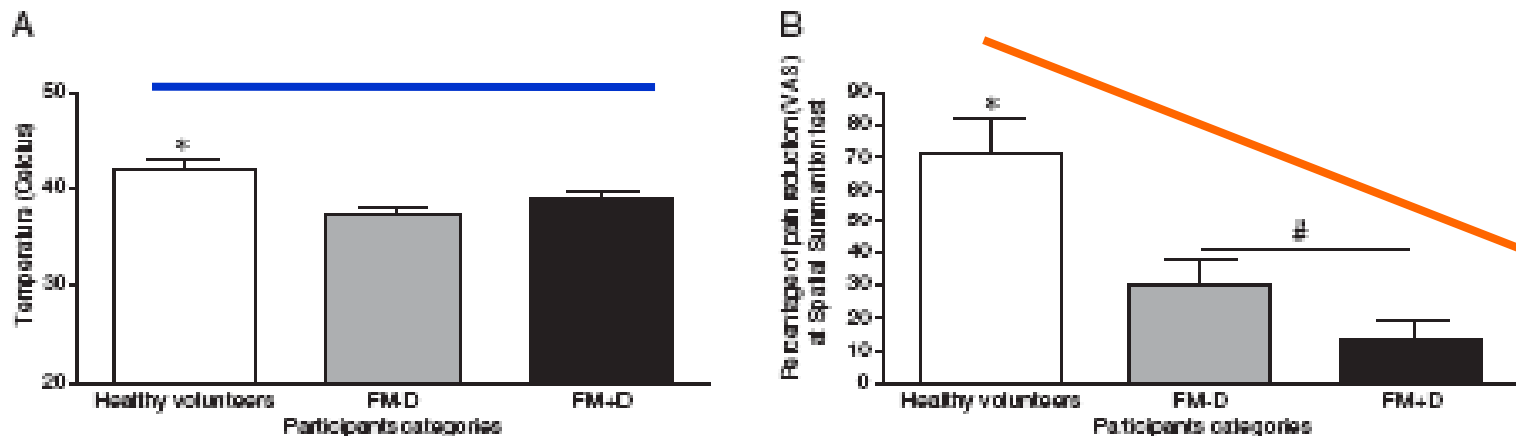
DNIC efficacy

(difference among FM-Subgroups when age was considered as a variable)

70% HW

30% FM-Type I

14% FM-Type II



* significant differences (P<0.05) between healthy volunteers and fibromyalgia patients

significant differences (P<0.05) between fibromyalgia patients without depressive (FM-D) and fibromyalgia with depressive symptoms (FM+D)

FIGURE 2. Thermal pain thresholds and pain inhibition mechanisms in healthy volunteers and fibromyalgia patients with and without depressive symptoms. A, Heat pain threshold temperature, in Celsius; B, DNIC efficacy, in percentage of pain reduction measured with the spatial summation test. DNIC indicates diffuse noxious inhibitory control.

Is autonomic reactivity to pain
equivalent on FM-subgroups
patients?

Is autonomic reactivity to pain equivalent on FM-subgroups?

Fibromyalgia as a sympathetically maintained pain syndrome (Martinez-Lavin, M. 2004)

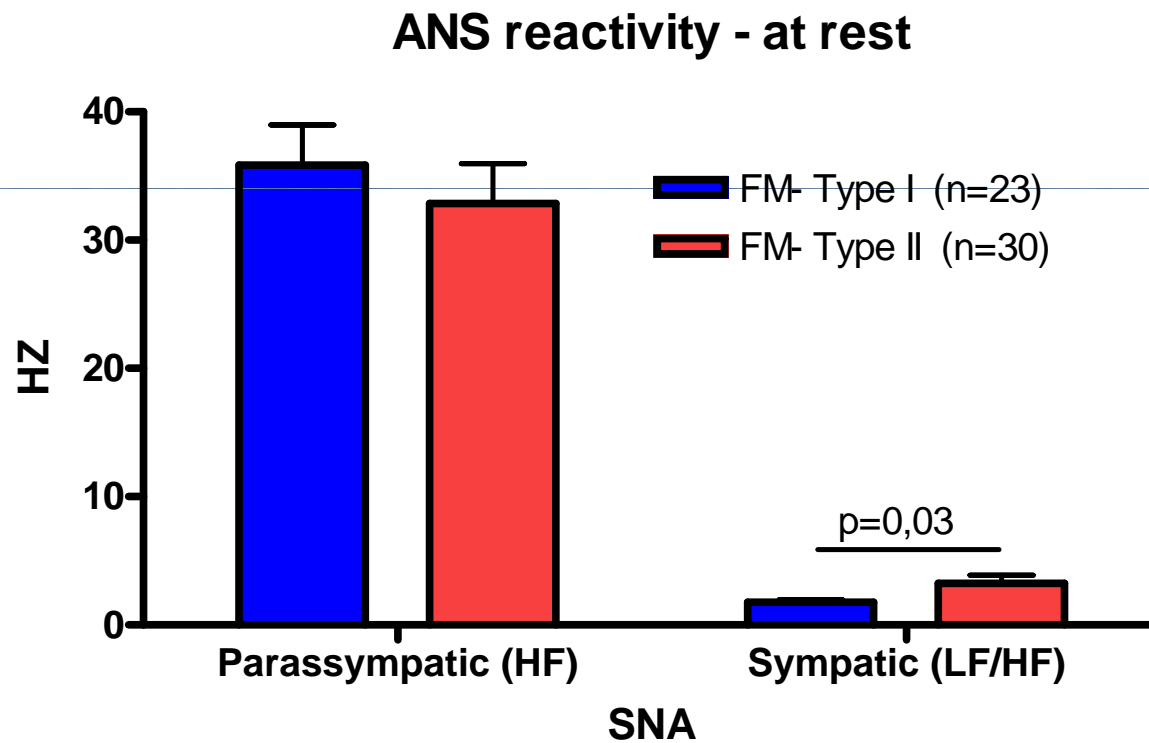
Pain = homeostatic response of the body

Nociceptive stimulus => changes in the Autonomic nervous system (sympathetic/ parasympathetic)

Autonomic reactivity to pain in fibromyalgia

	Subjects		p-value
	<i>FM</i>	<i>PM</i>	
	Mean \pm standard deviation		
HRV at rest			
<i>HF</i>	33.7 \pm 15.6	35.9 \pm 18.7	0.70
<i>LF</i>	60.5 \pm 17.8	58.7 \pm 18.7	0.81
<i>LF/HF ratio</i>	2.98 \pm 3.3	2.5 \pm 2.0	0.53
<i>Heart rate</i>	73.0 \pm 7.8	72.5 \pm 9.34	0.60
HRV during CPT			
<i>HF</i>	26.5 \pm 12.4	24.9 \pm 10.1	0.08
<i>LF</i>	64.6 \pm 16.9	65.9 \pm 17.2	0.12
<i>LF/HF ratio</i>	3.36 \pm 2.44	3.5 \pm 2.7	0.08
<i>Heart rate</i>	82.07 \pm 11.6	76.6 \pm 8.9	0.23

Autonomic reactivity to pain in FM-subgroups



HR

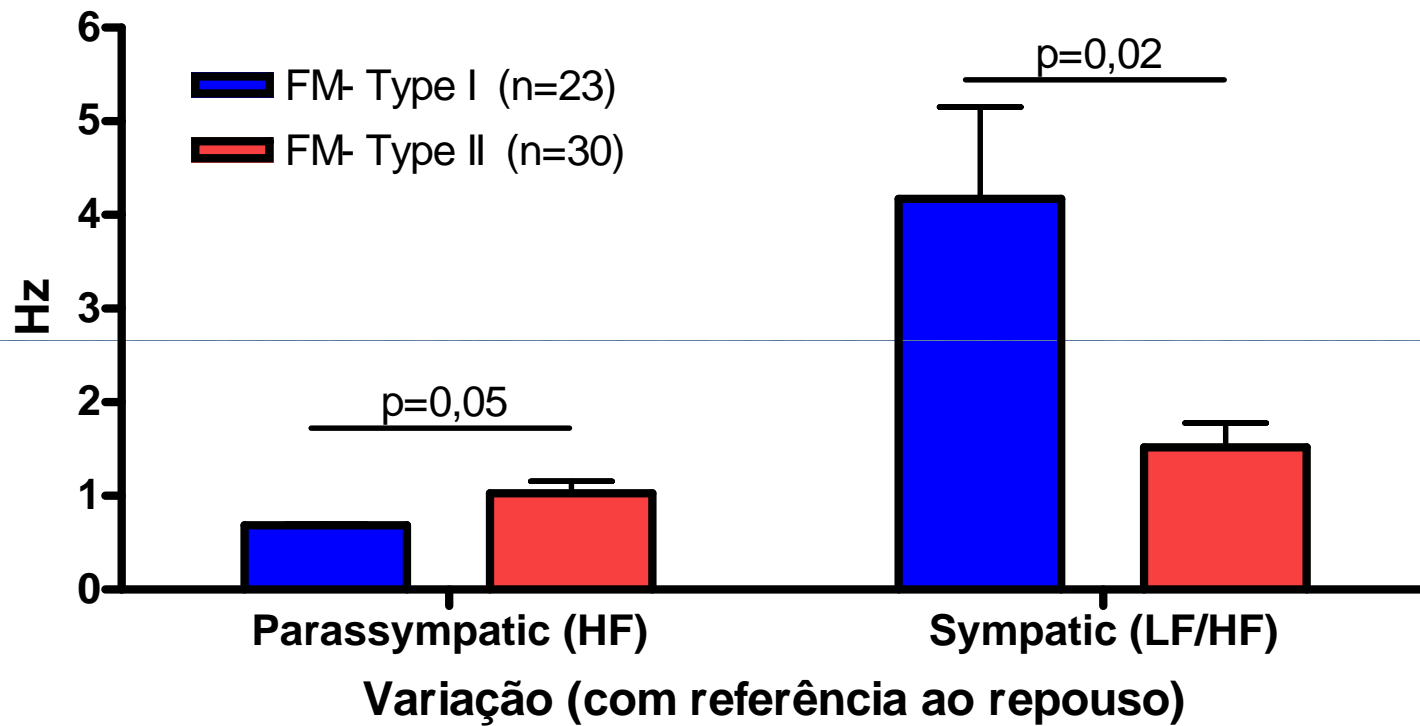
HR at rest

HR with PAIN or

80.0 (19)

84.1 (14)

Variation of ANS reactivity (painful stimuli)



Experimental pain (thermal)	FM- Type I (n=23)	FM-Type II (n=30)
VAS	75.4 (16)	76.8 (16.5)

Final considerations

FM – Type I and FM – Type II
Accessed by 6 VAS scale (from FIQ)

	FM- Type I	FM- Type II
Age (Tertiary Care Center)	Aged 53	Younger 47
Age (Community) $p=0.12$	51	48
Quality of life MCS-SF36	Moderate	Lower QoL
PCS	Moderate	Higher
Disability Index Clinical pain	Moderate Moderate	Higher Higher

Final considerations

FM – Type I and FM – Type II
Accessed by 6 VAS scale (from FIQ)

	FM- Type I	FM- Type II
Mood disorder	No	Yes
Pain + Stiffness + Fatigue	Lower/ Mod.	Intense
Morning Tiredness	Moderate	Intense
DNIC deficit (Serotonine/Noradrenaline and Enkefaline)	Moderate	High deficit
Autonomic reactivity to pain	Normal	Abnormal

ARE ISF EFFECT DIFFERENT
ON FM-SUBGROUPS?

ISF EFFECT IS EQUIVALENT ON FM-SUBGROUPS!

No statistical / clinical difference FM-
subgroups outcomes after ISF

Fm-subgroups improvement after ISF was
equivalent for both sub-groups
(depending variables: FIQ, PCS, PPT/TP,
SF-36, MPI)

Thank you



Florianópolis BRAZIL

Juliana.barcellos.de.souza@gmail.com